

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C12N 15/48, 7/01, A61K 39/21, C07K 16/10</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/09703</b> <b>(43) International Publication Date:</b> 24 February 2000 (24.02.00)
<b>(21) International Application Number:</b> PCT/CA99/00746 <b>(22) International Filing Date:</b> 12 August 1999 (12.08.99) <b>(30) Priority Data:</b> 60/096,235 12 August 1998 (12.08.98) US <b>(71) Applicant (for all designated States except US):</b> UNIVERSITY OF WESTERN ONTARIO [CA/CA]; Office of Industry Liaison, Stevenson-Lawson Building, Room 319, London, Ontario N6A 5B8 (CA). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KANG, Chil-Yong [CA/CA]; 111 Glenridge Crescent, London, Ontario N6G 4X9 (CA). LI, Yan [CA/CA]; 475 Ambleside Drive, London, Ontario N6G 4W9 (CA). <b>(74) Agent:</b> BERESKIN & PARR; 40 King Street West, 40th floor, Toronto, Ontario M5H 3Y2 (CA).			<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> HIV VACCINE			
<b>(57) Abstract</b>  A novel HIV vaccine is provided. In particular, the vaccine comprises an avirulent and non-cytolytic recombinant HIV wherein the NSS of the virus' envelope glycoprotein is replaced with a non-cytolytic signal sequence and <i>nef</i> gene of the virus is deleted which renders the virus avirulent.			

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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/CA 99/00746

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C12N15/48 C12N7/01 A61K39/21 C07K16/10

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 17825 A (UNIVERSITY OF CALIFORNIA) 18 August 1994 (1994-08-18) paragraph bridging pages 6 and 7 ---	1-31
A	B CHAKRABARTI ET AL: "A candidate live inactivatable attenuated vaccine for AIDS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 18, 3 September 1996 (1996-09-03), page 9810-9815 XP002077810 ISSN: 0027-8424 --- -/--	1-31

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

<sup>2</sup> Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 January 2000

Date of mailing of the international search report

20/01/2000

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Cupido, M

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 99/00746

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LI Y ET AL: "Effects of inefficient cleavage of the signal sequence of HIV-1 gp120 on its association with calnexin, folding, and intracellular transport" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 18, 3 September 1996 (1996-09-03), pages 9606-9611, XP002126656 WASHINGTON US page 9611, left-hand column, last paragraph</p> <p style="text-align: center;">---</p>	1-6
A	<p>LI Y ET AL: "Control of expression, glycosylation, and secretion of HIV-1 gp120 by homologous and heterologous signal sequences" VIROLOGY, vol. 204, no. 1, October 1994 (1994-10), pages 266-278, XP002126663 ORLANDO US</p> <p style="text-align: center;">-----</p>	1-6

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00746

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 25 and 26 insofar they concern an in vivo method, and claims 10-15 and 27-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the retrovirus.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out. specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00746

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417825 A	18-08-1994	AU 5848794 A	29-08-1994

A.P

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>9611-10</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 99/ 00746</b>	International filing date (day/month/year) <b>12/08/1999</b>	(Earliest) Priority Date (day/month/year) <b>12/08/1998</b>
Applicant <b>UNIVERSITY OF WESTERN ONTARIO et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**HIV VACCINE**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/ 00746

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 25 and 26 insofar they concern an in vivo method, and claims 10-15 and 27-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the retrovirus.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00746

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/48 C12N7/01 A61K39/21 C07K16/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 17825 A (UNIVERSITY OF CALIFORNIA) 18 August 1994 (1994-08-18) paragraph bridging pages 6 and 7 ---	1-31
A	B CHAKRABARTI ET AL: "A candidate live inactivatable attenuated vaccine for AIDS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 18, 3 September 1996 (1996-09-03), page 9810-9815 XP002077810 ISSN: 0027-8424 --- -/--	1-31

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## ° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

7 January 2000

Date of mailing of the international search report

20/01/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk  
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Fax: (+31-70) 340-3016

Authorized officer

Cupido, M

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 99/00746

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LI Y ET AL: "Effects of inefficient cleavage of the signal sequence of HIV-1 gp120 on its association with calnexin, folding, and intracellular transport" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 18, 3 September 1996 (1996-09-03), pages 9606-9611, XP002126656 WASHINGTON US page 9611, left-hand column, last paragraph</p> <p>---</p>	1-6
A	<p>LI Y ET AL: "Control of expression, glycosylation, and secretion of HIV-1 gp120 by homologous and heterologous signal sequences" VIROLOGY, vol. 204, no. 1, October 1994 (1994-10), pages 266-278, XP002126663 ORLANDO US</p> <p>-----</p>	1-6

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00746

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417825 A	18-08-1994	AU 5848794 A	29-08-1994

REC'D 14 NOV 2000

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference 9611-10	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CA99/00746	International filing date (day/month/year) 12/08/1999	Priority date (day/month/year) 12/08/1998
International Patent Classification (IPC) or national classification and IPC C12N15/48		
Applicant UNIVERSITY OF WESTERN ONTARIO et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  22/02/2000	Date of completion of this report  10.11.2000
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Huber, A  Telephone No. +49 89 2399 8173



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00746

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

### Description, pages:

1-19 as originally filed

### Claims, No.:

1-30 as received on 06/10/2000 with letter of 06/10/2000

### Drawings, sheets:

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA99/00746

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 9-14, 22-30 (IA).

because:

- ☒ the said international application, or the said claims Nos. 9-14, 22-30 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.  
☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N) Yes: Claims 1-21, 24, 26-30

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00746

	No:	Claims	22, 23, 25
Inventive step (IS)	Yes:	Claims	1-21, 24, 26-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8, 15-21
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**Re Item I**

**Basis of Report**

The sequence listings pages 1-3, filed with letter of 05.12.99, do not form part of the application (Rule 13 *ter.* 1(f) PCT)

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 9-14 and 22-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 9-14 and 22-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The present application relates to a non-cytolytic retrovirus, in particular HIV-1, wherein the natural signal sequence (NSS) has been replaced or modified. The retrovirus can be further rendered avirulent by deletion of the nef gene. The retrovirus can be used as a vaccine.

The application further relates to methods of killing a target cell, of preventing



apoptosis by administering an antagonist of HIV-1 NSS protein as well as to a method of inhibiting the effects of HIV-1 NSS.

2. Reference is made to the following documents:

D1: LI Y ET ALC: 'Control of expression, glycosylation, and secretion of HIV-1 gp120 by homologous and heterologous signal sequences' VIROLOGY, vol. 204, no. 1, October 1994 (1994-10), pages 266-278, XP002126663  
ORLANDO US

D2: LI Y ET AL: 'Effects of inefficient cleavage of the signal sequence of HIV-1 gp120 on its association with calnexin, folding, and intracellular transport' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 18, 3 September 1996 (1996-09-03), pages 9606-9611, XP002126656 WASHINGTON US

3. D1 and D2 disclose the recombinant expression in Sf9 cells of a baculovirus transformed with HIV-1 gp 120 wherein the natural signal sequence (NSS) of the envelope glycoprotein gp120 is either replaced by a more efficient signal sequence, such as mellitin or IL-3 signal sequence or in which the positively charged amino acids in the natural signal sequence are substituted with neutral amino acids.

It was shown that these modifications promote more efficient folding, intracellular transport and secretion of the protein. In D2 it is speculated that inefficient targeting of the envelope protein to the cell surface due to the natural signal sequence is a mechanism that the virus has evolved to evade the immune system and to optimize viral production. The correlation of defective secretion of secretory proteins with a pathological was also known. The authors propose that further analysis of the effects of HIV-1 NSS will lead to a more complete understanding of the role of the signal sequence related to viral pathology (see D2, page 9611, last two paragraphs).

4. It was not known from the prior art that the modifications of the NSS of HIV-1 envelope glycoprotein actually result in a non-cytolytic HIV-1 virus. In none of the

cited documents a HIV, wherein the NSS is modified, has been disclosed.

Hence, the subject-matter of Claims 1-21 is considered novel in the sense of Art. 33(2) PCT.

Although there is an indication in D1 that the NSS of HIV gp 120 has a cytotoxic effect on the target cell, as shown in insect cells infected with a recombinant baculovirus, there is no suggestion in D1 or in any other cited document to prepare a modified HIV-1 with an altered, non-cytotoxic signal sequence and that such a modified HIV-1 could be used as a non-cytolytic vaccine.

In view of the prior art, the skilled person could therefore not have reasonably expected that replacement or modification of the NSS of HIV-1 with a non-cytolytic signal sequence would result in a non-cytolytic HIV-1.

Hence, an inventive step can be acknowledged for the subject-matter of Claims 1-21.

Also the methods of Claims 26 (method of preventing apoptosis induced by the NSS of HIV-1 protein by administering an effective amount of antagonist to the HIV-1 NSS protein) and of Claim 29 (method of inhibiting the effects of the NSS of HIV-1 by administering an effective amount of an antisense oligonucleotide) have neither been disclosed nor rendered obvious in the cited prior art.

Therefore, also the subject-matter of Claims 26-30 is considered novel and to involve an inventive step (Art. 33(2) and (3) PCT).

5. Claim 22 is directed to method of killing a target cell comprising administering a recombinant virus containing NSS of HIV-1.

D1 discloses that 90% of SF9 cells infected with a recombinant baculovirus comprising the natural signal sequence of gp120 of HIV-1 were lysed, whereas 80-90 % of the cells infected with recombinant baculovirus without the signal sequence or substituted with a heterologous signal sequences remained intact. The authors conclude that the NSS of HIV-1 gp 120 may have a lethal effect on the cells (see D1, page 271, left col. I. 5-13). Hence the subject-matter of Claims 22, 23 and 25 is not novel in view of D1.

The use of VSV as the recombinant virus in the method of Claim 22 has neither been disclosed nor suggested in the prior art. Novelty and inventive step of Claim 24 is therefore acknowledged.

**Re Item VIII**

**Certain observations on the international application**

1. Claim 2 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. It would require undue burden of experimentation to determine how the NSS of HIV-1 has to be modified to render the virus non-cytolytic. Since a claim has to be clear from the wording of the claim alone, it is not sufficient that the technical features necessary to achieve the desired result are disclosed in the description. The same objection applies mutatis mutandis to Claims 10 and 16.
  
5. A cytolytic effect has only been demonstrated for the signal sequence of HIV-1 envelope glycoprotein (see description, page 2, lines 25-27), but not for any other HIV signal sequence. It is therefore not plausible that the claimed methods can be performed with any signal sequence derived from a HIV-1 protein. Independent Claims 22, 25 and 29 are, however, directed to any HIV-1 signal sequence. The broad scope of said claims does not appear to be justified by the limited disclosure of the specification. The claims are therefore objected under Art. 6 PCT in that they lack specific support.

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
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in its capacity as elected Office

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## Applicant

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1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
22 February 2000 (22.02.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
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